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Ischemic placental disease and risks of perinatal mortality and morbidity and neurodevelopmental outcomes

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ABSTRACT

Preeclampsia, intrauterine growth restriction, and placental abruption are serious obstetrical complications that constitute the syndrome of ischemic placental disease and account for a disproportionate degree of perinatal morbidity and mortality. We review the risks of stillbirth and neonatal and infant mortality in relation to ischemic placental disease, focusing on population-based studies. We also review the risks of neonatal morbidity and neurodevelopmental outcomes in relation to ischemic placental disease. A synthesis of the findings of the relevant studies relating ischemic placental disease to adverse perinatal outcomes underscores two important observations. First, despite the low prevalence of each of the three obstetrical complications, all are associated with increased risks of adverse perinatal and infant outcomes, as well as neurodevelopmental deficits. Second, the burden of increased perinatal risks appears strongest during the preterm period. Efforts to reduce the risks of ischemic placental disease remain critically important and developing effective clinical interventions will be a target worthy for consideration.

Introduction

Ischemic placental disease is defined as a constellation of obstetrical complications that include preeclampsia, intrauterine growth restriction (IUGR), and placental abruption.[1] Although the prevalence of each of these conditions is fairly low, they confer significant burden to overall maternal morbidity and mortality. In addition, these complications are associated with disproportionately increased risks of perinatal morbidity and mortality. In fact, preeclampsia, IUGR, and abruption are implicated in well over half of all indicated preterm deliveries,[1,2] which in turn, is associated with increased perinatal mortality and morbidity. While the rate of obstetrical interventions (labor induction or prelabor cesarean) at preterm gestations in the US has increased,[3,4] such increases are associated with a reduction in the risk of stillbirth.[4–6] However, whether the increase in obstetrical interventions has resulted in a concurrent decline in the neonatal and infant mortality rates remains poorly understood.

This review is organized in two parts. We first discuss the risks of adverse perinatal outcomes, including preterm delivery and IUGR as well as risks of stillbirth and neonatal and infant

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mortality in relation to ischemic placental disease, focusing on studies that are population-based. In the second part, we review the risks of neonatal morbidity and adverse neurodevelopmental outcomes in relation to ischemic placental disease.

Perinatal mortality associated with ischemic placental disease

Preeclampsia

Preeclampsia is associated with increased risks of stillbirth and neonatal and infant mortality. Population-based studies in the Scandinavian countries and the United States have shown perinatal mortality rates in pregnancies exposed to preeclampsia to be about two-fold higher compared to normotensive pregnancies. Preeclampsia remains one of the most important indications for either a labor induction or a prelabor cesarean or both.[1,7] Therefore, if preeclampsia occurs early in pregnancy warranting an obstetrical intervention and resulting in preterm delivery, the risks of perinatal mortality in such pregnancies are compounded by both the underlying hypertensive disorder and early delivery.

A study from the Norwegian Birth Registry of 804,448 first-born singleton births at ≥24 weeks between 1967 and 2003 reported that the odds ratio for perinatal mortality from preeclampsia decreased temporally during the study period (Table 1).[8] Perinatal mortality rates in the period 1991–2003 were 8.6 per 1000 births among preeclamptic women and 5.8 per 1000 births among normotensive women (adjusted odds ratio = 1.5, 95% CI 1.2–1.8).[8] This odds ratio progressively diminished over time from 3.4 in 1967–1978 to 1.9 in 1979–1990 and 1.5 in 1991–2003. A study by Lisonkova and Joseph[9] evaluated 456,668 deliveries in the state of Washington between 2003 and 2008. In adjusted analysis, the odds ratio for perinatal mortality was higher for early-onset preeclampsia (20–34 weeks of gestational age) but not late-onset preeclampsia (≥34 weeks of gestational age). A study of United States natality data from 1995 to 2000 by Chen et al.[10] of 23,654,785 singleton births stratified pregnancy-induced hypertension into early preterm (24–32 weeks), late preterm (32–36 weeks), and term (≥37 weeks) deliveries. The authors found that after adjusting for gestational age, infant mortality (death up to 1 year of age) was decreased for early and late preterm infants and increased for term infants.[10]

A large population-based study of over 57 million births in the US also reported increased risks of stillbirth and early and late neonatal mortality among women with pregnancy-induced hypertension, with the increased risks more prominent in multiparous than primiparous women.[11] Other studies have similarly demonstrated that perinatal mortality may be lower among preterm births due to preeclampsia compared to other causes, with a reversal in risks at term gestational ages.[12,13]

Small for gestational age

Gardosi et al.[14] utilized a regional perinatal database in England to evaluate risk of stillbirth in 92,218 singleton pregnancies (Table 2). The analysis demonstrated increased risk for stillbirth with both detected and undetected intrauterine growth restrictions (IUGRs). Getahun et al.[15] found that small for gestational age (SGA) at <5 percentile was associated with increased risk for antepartum stillbirth in an analysis of 626,883 singleton Missouri births. In a multicenter French trial of 56,606 births, Ego et al.[16] found fetal growth restriction was associated with increased risk of both stillbirth and perinatal death. Evaluating United States natality data, Malloy and Freeman[17] found that risk of infant death from sudden infant death syndrome, sudden unexplained death in infancy, and other causes of infant death increased in infants born SGA. These studies are in agreement with other population-based research that has demonstrated that IUGR and SGA are associated with increased perinatal and infant death.[18,19] A trial of fetuses with primarily early-onset IUGR that randomized participants to immediate delivery or expectant management did not find any difference in overall perinatal mortality.[20]

Table 1 – Perinatal and infant mortality in the setting of preeclampsia.

References	Population	Diagnosis	Outcome	Adjusted OR/RR (95% confidence interval)
Basso et al.[8]	Norway			
	1967–1978	Preeclampsia	Perinatal mortality	3.32 (3.01–3.65)
	1979–1990			1.86 (1.60–2.15)
	1991–2003			1.48 (1.23–1.78)
Chen et al.[10]	United States	Early preterm PIH	Infant mortality	0.50 (0.56–0.63)
		Late preterm PIH		0.80 (0.73–0.87)
		Term PIH		1.08 (1.02–1.14)
Ananth and Basso[11]	United States	PIH primigravid women	Stillbirth	1.52 (1.40–1.64)
			Neonatal mortality	1.30 (1.18–1.43)
		PIH multigravid women	Stillbirth	2.24 (2.11–2.37)
			Neonatal mortality	1.64 (1.51–1.78)
Lisonkova and Joseph[9]	Washington state	Early preeclampsia	Perinatal mortality	8.38 (6.48–10.8)
		Late preeclampsia		1.19 (0.83–1.69)

OR, odds ratio; RR, risk ratio; PIH, pregnancy-induced hypertension.